

DR MARCO CABRAS (Orcid ID : 0000-0002-8240-5874)

PROFESSOR GIOVANNI LODI (Orcid ID : 0000-0002-0218-8292)

Article type : Review Article

**Treatment of angular cheilitis: a narrative review and authors' clinical experience.**

Marco Cabras<sup>1</sup>, Alessio Gambino<sup>1,2</sup>, Roberto Broccoletti<sup>1</sup>, Giovanni Lodi<sup>3</sup>, Paolo G. Arduino<sup>1</sup>.

<sup>1</sup>Department of Surgical Sciences, Oral Medicine Section, CIR-Dental School, University of Turin, Turin, Italy;

<sup>2</sup>Department of Mechanical and Aerospace Engineering, Politecnico of Turin;

<sup>3</sup>Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy.

**Short title:** narrative review on angular cheilitis treatments.

Computer system: Mac OS X, Version 10.13.2; Word-processor: Microsoft Word for Mac, Version 16.9.1

Corresponding Author:

Dr. Marco Cabras

Department of Surgical Sciences; CIR - Dental School.

School of Medicine, University of Turin.

Oral Medicine Unit, Via Nizza 230, I-10126 Turin (Italy).

Telephone: + 390116331522; Fax: +39011618639.

E-mail: [cabrasmarco300@gmail.com](mailto:cabrasmarco300@gmail.com)

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ODI.13183](https://doi.org/10.1111/ODI.13183)

This article is protected by copyright. All rights reserved

**ABSTRACT**

Angular cheilitis (AC) is a clinical entity first described in the XIX century, characterized by erythema, rhagades, ulcerations, and crusting of one or both lip commissures and perilabial skin, responsible of an unpleasant and painful discomfort. Aim of this manuscript was to examine and evaluate the therapeutic options actually available for AC. Despite antifungals being the first-line treatment for most of clinicians, very limited scientific evidence supports their reliability, with just two RCTs published between the '70s and the '80s. Furthermore, alternative topical treatments, various techniques of occlusal vertical dimension restoration, B-vitamin supplementation, anti-drooling prosthetic device and photodynamic therapy have been experimented and proposed, mostly in the form of case reports or case-series on a small number of individuals. Our group found in 1% isoconazole nitrate (ISN) and 0.1% diflucortolone valerate (DFV) ointment the most consistent AC treatment, due to the broad spectrum of ISN against many species of dermatophytes and bacteria, and the anti-inflammatory properties displayed by DFV. However, further and well-designed trials on larger samples of patients are needed to assess the differential profile of consistency of the treatments outlined in literature and claimed by the Authors of this paper.

**Keywords:** angular cheilitis, cheilitis, narrative review, treatment, outcome.

## **Introduction**

Angular cheilitis (AC) was first described in 1855 by Dr. Lemaistre (Lemaistre, 1855) with the term “perlèche”, from the French word “pourelcher” (to lick one’s lip), being characterized by aphthous-like ulcers at the corner of the lips forcing patients, especially children, to “lick their lips at any time”.

Today, AC is by far the most common term used in dental and dermatologic literature, suggesting an inflammation (suffix –itis) at the corner (angular) of the lips (Greek term “cheilos”).

Clinically, it is a frequent condition characterized by erythema, rhagades, ulcerations, and crusting of the lip corners and the adjacent skin, either in one commissure or both. This form is downright different from other well known possibly dysplastic labial diseases (Pilati *et al*, 2017).

The most comprehensive categorization of AC clinical spectrum was formulated in 1986 by Ohman and co-workers. Small rhagades limited to the corner lips with slight skin involvement were defined as Type I; deeper and more extensive lesions with uneven borders were described as Type II; several rhagades extending from the lip corners into the perioral skin were referred as Type III. Finally, a diffuse erythema spread in the skin surrounding the vermilion border would fall into Type IV (Ohman *et al*, 1986). To date, this classification is still considered reliable and exhaustive, as the most recent case-series show (Oza and Doshi, 2017).

The aetiology of AC is extremely varied, with many local and/or systemic causes responsible for first onset and recurrence. Clinical experience suggests a direct link between insufficient or inappropriate support of the lip corners and AC appearance, through salivary stasis and maceration of the commissures. In this sense, reduced vertical dimension caused by edentulism or ill-fitting dentures, weight loss, malnutrition, smoking and mouth breathing can be recalled as local causes of AC (Park, Brodell, and Helms, 2011).

Among the iatrogenic causes, orthodontic treatment (Cross and Short, 2008; Cross *et al*, 2010) and surgical procedures such as tonsillectomy have been described (England *et al*, 1999), with nickel-based braces being potentially responsible for an allergic form (Yesudian and Memon, 2003).

*Candida albicans*, *Streptococcus aureus* and *Streptococci* are commonly associated with AC, with the former being cultured since the 1920s (Finnerud, 1929; Schoenfeld and Schoenfeld, 1977; Schwab and Brasher, 1977; Ohman *et al*, 1986; Warnakulasuriya *et al*, 1991): pseudo hyphae and budding yeasts have been detected in 48% (Warnakulasuriya *et al*, 1991) up to 93% of cases (Schoenfeld and Schoenfeld, 1977).

Concerning the systemic causes, nutritional deficiencies such as iron, riboflavin, thiamin, and cobalamin deficiencies have been investigated since the 1960s (Mäkilä, 1969; Murphy and Bissada, 1979), being still an issue to this day, particularly among children in developing countries, where AC can arise as one of the several signs of malnourishment (Kaur and Goraya, 2018).

Similarly, all the systemic causes of xerostomia – Sjögren syndrome, diabetes mellitus, radiotherapy of head-and-neck district, salivary neoplasms, neurological disorders, drugs – must be recollected in the differential diagnosis (Błochowiak *et al*, 2016; Skiba-Tatarska *et al*, 2016).

Genetic disorders such as Down syndrome may be associated with recurrent *Candida*-mediated AC (Ercis *et al*, 1996; Scully *et al*, 2002), as well as autoimmune bullous diseases (Caetano *et al*, 2015), orofacial granulomatosis (McCartan *et al*, 2011), and Crohn's disease (Howell *et al*, 2012) where AC can even occur as the initial sign of the underlying disease (Bangsgaard *et al*, 2011).

Some systemic infections, such as secondary syphilis, have been correlated with AC, where false forms may arise (Eyer-Silva *et al*, 2017), and HIV/AIDS, where differences in the AC flora can be found between seronegative and seropositive patients (Krishnan and Kannan, 2013).

Finally, AC may be a side effect of drug assumption. Paroxetine (Verma *et al*, 2012), tetracyclines (McKendrick, 1968) and metronidazole can trigger the condition, being the latter responsible of an unusual association of AC and aphthous-like ulcers (Hushan and Bhushan, 2016). Moreover, changes in skin fragility, triggered by isotretinoin, can lead to AC elicited by *Staphylococcus aureus* (Graham *et al*, 1986). Among biologic agents, it is worth mentioning secukinumab, which can be responsible for persistent forms of AC due to its ability to suppress keratinocyte proliferation and differentiation (Hitaka *et al*, 2018).

In light of such an extensive combination of multiple factors, we tried to conduct a review of the literature concerning AC therapeutic approaches, with the aim of assessing if there is any solid experimental evidence behind the most commonly prescribed treatments.

## **Methods**

From June 2018 to November 2018, two researchers (PGA and RB) conducted a review on the treatment of AC. No initial restriction has been posed concerning the date of publication. Inclusion criteria were as follows: case reports, case-series, open clinical trials and Randomized Controlled

Trials (RCTs) written in English, conducted on human patients, with clinical and/or microbiological features of angular cheilitis, undergoing a specific treatment carried out by dentist/oral physician/dermatologist.

Exclusion criteria were applied to articles published in a language other than English, reviews concerning the treatment of angular cheilitis, and "non-inherent" studies, defined as such when:

- not performed on human patients whatsoever;
- describing other forms of microbial or allergic cheilitis;
- not mentioning fungal cheilitis in any way;
- reviewing or describing causes and/or pathogenesis of fungal cheilitis without discussing treatment of such condition.
- Reports of allergy or drug-induced AC, where the mere withdrawal from the allergen or drug was enough to provide complete remission of signs and symptoms of AC.

The research was conducted on Google Scholar, as well as the following electronic databases: Cochrane Library, NIH (National Institute of Health), PubMed, Scopus, Up To Date, Web of Science.

The initial search comprised the MeSH terms "Angular Cheilitis Treatment" "Angular Cheilitis Therapy". The complete search strategy used for PubMed electronic database was angular [All Fields] AND ("cheilitis"[MeSH Terms] OR "cheilitis"[All Fields]) AND ("therapy"[Subheading] OR "therapy"[All Fields] OR "treatment"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]). Initially, no language restrictions were applied, aiming to exclude non-English studies in the first phase of study selection. On the contrary, no restriction regarding the publishing year was carried out.

## **Results**

Two reviewers (PGA and RB) independently identified 3313 articles, classified as follows: 1646 duplicates, 1590 not inherent for the aim of our work, 65 published in other-than-English, 6 case-reports, 3 case-series, 2 RCTs, 1 open clinical trial. Due to the very limited amount of evidence available, a narrative description of each treatment has been provided.

The following treatments have been described: topical treatments (Table 1), occlusal vertical dimension (OVD) restoration techniques (Table 2), other treatments (anti-drooling prosthetic rehabilitation, vitamin supplementation and photodynamic therapy, Table 3).

## **Topical treatments**

### *Silicone-based oils*

Topical application of silicone oils has been attempted in the 1950s (Reiches, 1953) in a small case-series of 13 patients (of which 5 with ill-fitting dentures, affected by AC not caused by ariboflavinosis); a “silicote” ointment (compounded of 30% silicone oils in a petrolatum base), containing 3% boric acid or 2% ammoniated mercury, showed promising results among the eight patients with no prosthetic issues, and the healing was reached after three to eight days. On the other hand, four of the five patients with unsuitable dentures had good results, with one experiencing a recurrence one week after the conclusion of treatment. The main limits of this case-series lied on the limited sample of patients enrolled, the lack of details regarding the posology of the ointment as well as for the definition of healing, which appears to be unclear.

#### *Antifungal agents*

In 1975, a randomized single-blinded control trial was published (Nairn, 1975), in which 46 patients with AC and/or denture stomatitis were randomly split in three groups of 13, 18 and 15 individuals. Each patient was blindly treated for one month by sucking a tablet four times a day containing 500000 U of nystatin, 10 mg of amphotericin B, or a placebo made of heat-denatured fungilin lozenges, respectively.

After one month, 77% (10/13) of patients in the first group and 89% (16/18) of patients in the second group showed a complete clinical remission, with only 40% (6/15) of healing in the placebo-group. This study carried some limitations, such as the discrepancy in sample size between the 52 patients reported in “Methods” and 46 patients whose results were described, the smallness of the sample precluding comparison between nystatin and amphotericin B, lack of details concerning intra-perioral recurrence found in 16 of 31 patients one month after the end of the antimycotic medications. However, this trial had the merit of giving, for the first time in literature, evidence about the role of *Candida albicans* in the pathogenesis of AC.

In 1988, an open and a double-blind study on 58 patients with AC was published (Ohman and Jontel, 1988). More in detail, while 50 patients were divided in four groups according to the original microbial sampling, either *C. albicans*, *S. aureus*, or both, and openly treated either with nystatin, fusidic acid or both, eight patients with bilateral and clinically identical type 2 AC, infected only with *C. albicans*, were enrolled in a double-blind study. Therefore, they were given two undistinguishable tubes of ointment (nystatin 100,000 IU/g vs placebo), labelled with a red or green marker, depending on which side they were to be used, and instructed to apply both devices four times a day. Moreover, patients were urged to wear rubber gloves and to change them between the applications, in order to minimize contamination on each site. With healing defined as a combination of disappearance of signs of inflammation and negative microbial sampling for *C.*

albicans, nystatin appeared to be significantly more effective than placebo ( $p < 0.001$ ), with all sites treated with the antifungal device being able to heal completely after four weeks of treatment, and no growth of *C. albicans* detected one week after clinical remission. On the other hand, only one of the eight commissures treated with placebo achieved complete healing.

Despite the significant difference obtained through Fisher's exact probability test, the main limits of this RCT rely in the very limited number of patients admitted to the random approach, which is a consequence of the peculiar eligibility criteria chosen by the Authors, with bilateral and clinically identical AC being the sine qua non condition required for enrolment in the study.

In 2008, a small case series of young patients affected by AC (Cross and Short, 2008) during orthodontic treatment showed contrasting results regarding miconazole nitrate 2% gel when applied on the affected commissures. Two of the three patients enrolled in this study were instructed to apply it four times a day for two weeks, with one individual achieving complete remission after one session, while the other was instructed to repeat it twice to no avail, leading to the interruption of the fixed orthodontic treatment. With just two patients enrolled and such a split result between them, no univocal evidence can be inferred.

#### *Pimecrolimus*

A unique case of plasma cell angular cheilitis was published in 2014 (da Cunha Filho *et al*, 2014), with a 58 years old man presenting with an asymptomatic, red-purplish ulcerated plaque in the right commissure, unresponsive to antibiotic and antifungal topical treatments.

An incisional biopsy was carried out, showing a normal epidermidis with a dense dermal infiltrate of lymphocytes, neutrophils and an unusual infiltration of mature plasmocytes. After unsuccessful infiltration with triamcinolone and cryosurgery, pimecrolimus topical cream application twice a day finally lead to an almost complete remission, after 90 days of treatment. The main limit of this study lies in its own uniqueness, with no other case of "plasma cell" angular cheilitis reported within this very case-report or in literature to rely on for comparison.

#### *Ozonized olive oil*

The reliability of ozonized olive oil in treating various oral lesions was tested in a recent clinical trial of 50 patients (Kumar *et al*, 2016), of which ten with AC: twice a day topical application was successful in each one of these patients, with a mean of 2.3 days to reach complete healing. The small size of the sample, as well as the shortage of information regarding the clinic and/or microbiologic characteristics of AC before treatment are the main limitations of this protocol.

## **Occlusal vertical dimension (OVD) restoration techniques**

### *Surgery*

A small case-series of eight patients was published in 1971, (Symington, 1971) proposing a surgical correction of AC, as an alternative for those individuals with chronic and discomforting AC, especially if not-responding to the removal of the local and haematological abnormalities and application of antifungal creams. The operative procedure, performed under general anaesthesia in six cases, consisted of excision of the affected area, preserving the underlying muscle coat, followed by the delineation of a vertical mucosal flap, which was then rotated, raised, turned into the initial defect and sutured. An additional suture was performed to close the vertical defect by direct approximation of the edges. Such technique displayed encouraging results, with seven patients exhibiting post-operative healing, and five individuals with no recurrence after two years. The main limit of this study lies in the operator-dependency of such technique, which also required hospitalization of 75% of these patients, as well as the small number of patients enrolled. Moreover, surgery for a recurrent microbiological condition should not be proposed, differently from other labial conditions (Carvalho *et al*, 2019).

### *Collagen implants*

In the 1980s, (Chernosky, 1985) injection of collagen implants was pursued in two patients with a decreased vertical facial dimension. Purified bovine collagen implant (Zyderm®) was injected in the depths of the commissures, with no recurrences in the subsequent three and eight months of follow-up. The main limit of the paper resides in the sheer scarcity of patients involved, with no further studies by the same Authors or Others experimenting again with this protocol.

### *Hyaluronic acid dermal fillers*

A case-report of an 80-year-old patient with recurrent bilateral AC unresponsive to topical antimycotics was described in 2018. (Lorenzo-Pouso AI, García-García A, Pérez-Sayáns M, 2018). In this case, due to the reluctance of the patient to undergo prosthodontics treatment, a nonsurgical facial aesthetics (NSFA) technique was proposed. After bilateral intraoral mental nerve block, hyaluronic acid dermal filler (Surgiderm 30; Inibsa) was injected in both mentolabial sulci with a 28-gauge needle. The patient experienced an immediate relief with no recurrence of AC in the next 12 months. As emphasised by the Authors, the main limitations of this approach consist in the accuracy of patients' enrolment, due to the absolute and relative contraindication related to NSFA techniques, as well as the high level of training required by the oral physician.



## **Other treatments**

### *Vitamin supplementation*

Although a large case-series of 339 patients (Makila, 1969), of which 61 with AC, detected significantly lower values of serum thiamine ( $p < 0.05$ ), free riboflavin ( $p < 0.02$ ) and dietary intake of iron in these patients when compared to controls, there is very low evidence concerning a cause-effect relationship between vitamin supplement and resolution of AC.

In this sense, our research lead to one case-report published in 1979, where a 25 years old pregnant woman with iron deficiency anaemia and AC was successfully treated with two capsules twice a day of ferrous sulphate (Murphy and Bissada, 1979). The study design and the lack of information regarding duration of treatment represent the main limitations; to our knowledge, no other case of AC strictly related to iron deficiency anaemia has been reported.

### *Anti-drooling prosthetic rehabilitation*

A case-report of exclusively prosthodontic management for persisting AC and salivary drooling in an 87 years-old woman was described (Lu, 2007). A mandibular removable prosthesis was forged, with occlusal splints of various thicknesses tested in order to restore an appropriate and comfortable vertical dimension of occlusion. However, since this alone was not sufficient to eradicate drooling, a catheter device was carved within the left flange in order to pool the saliva in the oropharyngeal area, thus facilitating swallowing. With this additional device, drooling ended and AC did not recur. The anecdotal nature of evidence, with no follow-up available, and the high prosthodontic expertise required to carry out such a tailored rehabilitation represent the main limits of this report.

### *Photodynamic therapy*

In 2016, (Rocha *et al*, 2016) a case-report described the treatment with photodynamic therapy (aPDT) in a 28 years-old diagnosed with acute lymphoblastic leukaemia suffering from AC at the right commissure. After the application of Methylene Blue 0.01% for five minutes, aPDT was performed with a continuous diode laser irradiation, 660 nm, with a dose of  $120 \text{ J/cm}^2$ , 120s (one point), 4.8J, 40mW,  $1 \text{ W/cm}^2$  and spot size  $0.04 \text{ cm}^2$ , leading to an immediate pain relief and re-epithelization of the site. The study design itself, with only one patient enrolled in this protocol, as well as the cost-effectiveness of aPDT, represent its main limits.

## **Discussion**

Bearing in mind the complexity of AC etiopathogenesis, aim of the present report was to provide a narrative description of the treatments available for AC.

With only two RCTs available, both published before the 1990s (Nairn, 1975; Ohman and Jontel, 1988), it seems appropriate to state that, to date, there are no sufficient data to establish which treatment is more reliable in managing AC in the everyday clinical practice.

Moreover, all of the aforementioned therapeutic alternatives to antifungals throughout the last six decades cannot be considered reliable, being discussed in either isolated case reports, small case-series or open trials, with samples ranging between eight and 20 patients.

In our everyday clinical practice, vitamin deficiency is rarely the main cause of AC: furthermore, whenever a vitamin deficiency is present as an underlying condition, AC is not the only oral pathology that can be encountered. Usually, a more comprehensive pattern arises, inclusive of tongue atrophy, candidiasis, aphthous-like ulcers, and burning sensation or sore mouth. Therefore, vitamin supplements alone seem not to be an appropriate therapy for most cases of AC.

Similarly, surgical approaches or silicone-based oils should not be considered a first line of treatment: the former, due to the sheer imbalance between risks, such as the necessity of general anaesthesia, and potential benefits; the latter, due to the more promising efficacy of ointment or oils exhibiting antibacterial and antifungal properties.

Photodynamic therapy and NSFA seem to be highly limited approaches, since both demand detailed understanding and intensive training, which are not going to be achieved by the vast majority of general practitioners, nor are they required in the everyday clinical practice.

Moreover, pimecrolimus, as an immunosuppressor, should be reserved only in case of an AC unresponsive to antibiotics and antifungals, in which the inflammatory nature is confirmed through biopsy, in order to avoid a paradoxical worsening of clinical signs and symptoms.

In absence of robust evidence from literature, the Authors' still rely on their clinical experience: it is Authors' personal opinion that the topical treatment with antifungals combined with corticosteroids is the most reliable therapeutic option against AC, combined with denture relining, if needed.

More specifically, during the last ten years of clinical practice, our group found in a specific ointment (e.g. 1% isoconazole nitrate and 0.1% diflucortolone valerate) the utmost consistency in providing a speedy recovery from AC, with a posology of two applications per day for 2 weeks. Isoconazole nitrate (ISN) has been used successfully in the treatment of dermatomycoses (Havlickova and Friedrich, 2008; Veraldi, 2013), a well-known clinical entity among dermatologists, which shares part of the microbial and fungal aetiology attributed to AC, being triggered by dermatophytes and frequently superinfected by bacteria of *Staphylococcus* species. ISN alone seems to exhibit a broad spectrum against many species of dermatophytes (Yang *et al*, 2008), such as *Microsporum* spp., *Trichophyton* spp., *Epidermophyton* spp., and yeasts, such as

*Candida albicans*, *Candida parapsilosis*, *Candida kruzei* (Havlickova and Friedrich, 2008), through reduction of adenosine triphosphate (ATP) (Odds *et al*, 1985) and inhibition of synthesis of ergosterol (Fromtling, 1988).

On the other hand, *in vitro* evidence showed antibacterial activity of ISN against *Staphylococcus aureus*, *Staphylococcus haemolyticus*, up to methicillin-resistant *Staphylococcus aureus* through the production of reactive species of oxygen (ROS), and specifically singlet oxygen, thus triggering apoptosis (Czaika *et al*, 2013).

When combining ISN with a topical corticosteroid, such as diflucortolone valerate (DFV), further benefits can occur: apart from the immediate relief from symptoms mediated by inflammation, such as itching and erythema, vasoconstriction caused by DFV might lead to an enhanced concentration of ISN in the muco-cutaneous site. Furthermore, the corticosteroid itself can reduce the symptoms of hypersensitivity from the antifungal itself ignited by the release of fungal toxins (Havlickova and Friedrich, 2008). A review on the clinical application and safety of 1% ISN plus 0.1% DFV for dermatomycoses underlines the triple-action profile based on the data from four decades of clinical experience and various clinical trials, and the remarkable profile of safety, with only 19 medically confirmed adverse drug reaction case reports recorded in more than twenty years of post-marketing surveillance (Veraldi, 2013).

In light of the limited evidence available in literature for alternative treatments, our group is committed in conducting randomized clinical trials involving the 1% ISN and 0.1% DFV ointment as experimental treatment for patients with AC, in order to assess if such a solid consistency in the dermatological field can be also reproduced and observed on perioral and intraoral lesions.

Further and larger randomized controlled studies are in fact needed to shed light on the true weight of an antimycotic therapy in the management of AC, either alone or combined with topical corticosteroid, with particular attention needed for chronic and recurrent AC, which seem to hide a multifactorial etiopathogenesis.

The present review showed lack of evidence regarding AC therapy, despite its frequent prevalence in the population, especially among the elderly. Further studies are needed to assess if novel therapeutic approaches may replace the antimycotic formulation, which, despite the scarcity of evidence, are by far the most frequently prescribed. An appropriate evaluation of the patient's general health and a thorough investigation of the underlying local factors is essential, since its underestimation might contribute not only to the onset but also, and more importantly, to the recurrence of AC.

#### **Author contribution**

All the Authors were involved in the design of the study. PGA and RB conducted the database searches and drafted the paper. PGA, MC and GL analyzed the data. All of the authors were involved in writing the manuscript.

### **Conflicts of interest**

None.

### **Funding**

No financial support.

### **References**

Bangsgaard N, Weile B, Skov L (2011). Organised angular cheilitis as the initial sign of Crohn's disease in two children. *Acta Derm Venereol* 91: 207-208.

Błochowiak K, Olewicz-Gawlik A, Polańska A, Nowak-Gabryel M, Kocięcki J, Witmanowski H, Sokalski J (2016). Oral mucosal manifestations in primary and secondary Sjögren syndrome and dry mouth syndrome. *Postępy Dermatol Alergol* 33: 23-27.

Caetano Lde V, Enokihara MM, Porro AM (2015). Recurrent angular cheilitis in a patient with mucocutaneous pemphigus vulgaris. *Clin Exp Dermatol* 40: 819-821.

Carvalho MV, de Moraes SLD, Lemos CAA, Santiago Júnior JF, Vasconcelos BCDE, Pellizzer EP (2019). Surgical versus non-surgical treatment of actinic cheilitis: A systematic review and meta-analysis. *Oral Dis* 25: 972-981.

Chernosky ME (1985). Collagen implant in management of perlèche (angular cheilosis). *J Am Acad Dermatol* 12: 493-496.

Cross DL, Short LJ (2008). Angular cheilitis occurring during orthodontic treatment: a case series. *J Orthod* 35: 229-233.

Cross D, Eide ML, Kotinas A (2010). The clinical features of angular cheilitis occurring during orthodontic treatment: a multi-centre observational study. *J Orthod* 37: 80-86.

Czaika VA, Siebenbrock J, Czekalla F, Zuberbier T, Sieber MA (2013). Reactive oxygen species and the bacteriostatic and bactericidal effects of isoconazole nitrate. *Mycoses* 56: 16-22.

da Cunha Filho RR, Tochetto LB, Tochetto BB, de Almeida HL Jr, Lorencette NA, Netto JF (2014). "Angular" plasma cell cheilitis. *Dermatol Online J* 20.

England RJ, Lau M, Ell SR (1999). Angular cheilitis after tonsillectomy. *Clin Otolaryngol Allied Sci* 24: 277-279.

Ercis M, Balci S, Atakan N (1996). Dermatological manifestations of 71 Down syndrome children admitted to a clinical genetics unit. *Clin Genet* 50: 317-320.

Eyer-Silva WA, Freire MAL, Horta-Araujo CA, Almeida Rosa da Silva G, Francisco da Cunha Pinto J, Raphael de Almeida Ferry F (2017). Secondary syphilis presenting as glossodynia, plaques en prairie fauchée, and a split papule at the oral commissure: case report and review. *Case Rep Med* ID:1980798.

Finnerud CW (1929). Perlèche. A clinical and etiologic study of one hundred cases. *Arch Derm Syphilol* 20: 454-488.

Fromtling RA. (1988). Overview of medically important antifungal azole derivatives. *Clin Microbiol Rev* 1: 187-217.

Graham ML 2nd, Corey R, Califf R, Phillips H (1986). Isotretinoin and Staphylococcus aureus infection. A possible association. *Arch Dermatol* 122: 815-817.

Havlickova B, Friedrich M (2008). The advantages of topical combination therapy in the treatment of inflammatory dermatomycoses. *Mycoses* 51: 16–26.

Hitaka T, Sawada Y, Okada E, Nakamura M (2018). Recurrent angular cheilitis after secukinumab injections. *Australas J Dermatol* 59: e79-e80.

Howell JL, Bussell RM, Hegarty AM, Zaitoun H (2012). Service evaluation of patients with orofacial granulomatosis and patients with oral Crohn's disease attending a paediatric oral medicine clinic. *Eur Arch Paediatr Dent* 13: 191-196.

Hushan A, Bhushan STV (2016). Metronidazole induced aphthous ulcer with angular cheilitis. *Pharm Pharmacol Int J* 4: 350–351.

Kaur S, Goraya JS. Dermatologic findings of vitamin B12 deficiency in infants. *Pediatr Dermatol* 35: 796-799.

- Krishnan PA, Kannan R. Comparative study on the microbiological features of angular cheilitis in HIV seropositive and HIV seronegative patients from South India. *J Oral Maxillofac Pathol* 17: 346-350.
- Kumar T, Arora N, Puri G, Aravinda K, Dixit A, Jatti D (2016). Efficacy of ozonized olive oil in the management of oral lesions and conditions: A clinical trial. *Contemp Clin Dent* 7: 51-54.
- Lemaistre J (1855). Etude sur fair de la vile de lemerges de la perleche: du Streptococcus plicatilis. *Éc. préparatoire de méd. et de pharm.*
- Lorenzo-Pouso AI, García-García A, Pérez-Sayáns M (2018). Hyaluronic acid dermal fillers in the management of recurrent angular cheilitis: A case report. *Gerodontology*. 35:151-154. doi: 10.1111/ger.12329.
- Lu DP (2007). Prosthodontic management of angular cheilitis and persistent drooling: a case report. *Compend Contin Educ Dent* 28: 572-577.
- Mäkilä E (1969). Prevalence of angular stomatitis. Correlation with composition of food and metabolism of vitamins and iron. *Acta Odontol Scand* 27: 655-680.
- McCartan BE, Healy CM, McCreary CE, Flint SR, Rogers S, Toner ME (2011). Characteristics of patients with orofacial granulomatosis. *Oral Dis* 17: 696-704.
- McKendrick AJ (1968). Denture stomatitis and angular cheilitis in patients receiving long-term tetracycline therapy. *Br Dent J* 124: 412-417.
- Murphy NC, Bissada NF (1979). Iron deficiency: an overlooked predisposing factor in angular cheilitis. *J Am Dent Assoc* 99: 640-641.
- Nairn RI (1975). Nystatin and amphotericin B in the treatment of denture-related candidiasis. *Oral Surgery, Oral Surg Oral Med Oral Pathol* 40: 68-75.
- Odds FC, Cheesman SL, Abbott AB (1985). Suppression of ATP in *Candida albicans* by imidazole and derivative antifungal agents. *Sabouraudia* 23: 415-424.
- Ohman SC, Dahlén G, Möller A, Ohman A (1986). Angular cheilitis: A clinical and microbial study. *J Oral Pathol* 15: 213-217.
- Ohman SC, Jontel M (1988). Treatment of angular cheilitis: The significance of microbial analysis, antimicrobial treatment, and interfering factors. *Acta Odontol Scand* 46: 267-272.

- Oza N, Doshi JJ (2017). Angular cheilitis: A clinical and microbial study. *Indian J Dent Res* 28: 661-665.
- Park KK, Brodell RT, Helms SE (2011). Angular cheilitis, part 1: local etiologies. *Cutis* 87:289-95.
- Pilati S, Bianco BC, Vieira D, Modolo F (2017). Histopathologic features in actinic cheilitis by the comparison of grading dysplasia systems. *Oral Dis* 23: 219-224.
- Reiches AJ (1953). Angular stomatitis treated with silicote ointment. *AMA Arch Derm Syphilol* 68: 336-337.
- Rocha BA, Melo Filho MR, Simões A (2016). Antimicrobial Photodynamic Therapy to treat chemotherapy-induced oral lesions: Report of three cases. *Photodiagnosis Photodyn Ther* 13: 350-352.
- Schoenfeld RJ, Schoenfeld FI (1977). Angular cheilitis. *Cutis* 19: 213-216.
- Schwab JT, Brasher WJ (1977). Management of patients with angular cheilitis. *Gen Dent* 25: 43.
- Scully C, van Bruggen W, Diz Dios P, Casal B, Porter S, Davison MF (2002). Down syndrome: lip lesions (angular stomatitis and fissures) and *Candida albicans*. *Br J Dermatol* 147: 37-40.
- Skiba-Tatarska M, Kusa-Podkańska M, Surtel A, Wysokińska-Miszczuk J (2016). The side-effects of head and neck tumors radiotherapy. *Pol Merkur Lekarski* 41: 47-49.
- Symington JM (1971). A surgical treatment of angular cheilitis. *Br J Plast Surg* 24: 315-318.
- Veraldi S (2013). Isoconazole nitrate: a unique broad-spectrum antimicrobial azole effective in the treatment of dermatomycoses, both as monotherapy and in combination with corticosteroids. *Mycoses* 56: 3-15.
- Verma R, Balhara YP, Deshpande SN (2012). Angular cheilitis after paroxetine treatment. *J Clin Psychopharmacol* 32: 150-151.
- Warnakulasuriya KA, Samaranayake LP, Peiris JS. (1991) Angular cheilitis in a group of Sri Lankan adults: a clinical and microbiologic study. *J Oral Pathol Med* 20: 172-175.
- Yang W, Wiederhold NP, Williams RO 3rd (2008). Drug delivery strategies for improved azole antifungal action. *Expert Opin Drug Deliv* 5: 1199–1216.
- Yesudian PD, Memon A (2003). Nickel-induced angular cheilitis due to orthodontic braces. *Contact Dermatitis* 48: 287-288

**Table 1.** Available studies for topical treatments of AC

Reference	Type of study	Size of sample	Drug used	Main findings
Reiches et al (1953)	Case-series	13 patients with AC	“silicote” ointment (compounded of 30% silicone oils in a petrolatum base) containing 3% boric acid or 2% ammoniated mercury	Healing (undefined) after 3-8 days for 8 patients with no ill-fitting dentures; “good results” (undefined) for 4 patients with ill-fitting dentures;  Recurrence one week after discontinuation for one patient
Nairn et al (1975)	Randomized single-blinded control trial	46 pts Group 1: 13 Group 2: 18 Placebo group: 15	Group 1: 500000-U Nystatin tablets 4 times daily for one month  Group 2: 10-mg fungilin lozenges (Amph.B) four times daily for one month, with no dentures  Placebo group: heat-denatured fungilin	Group 1: 77% cured after one month  Group 2: 89% cured after one month  Placebo group: 40% cured



			lozenges (placebo) four times daily for one month	after one month  Not possible to establish a comparison between Nystatin and Amph.B
<b>Ohman et al (1988)</b>	Open/double-blind study	8 pts with identical (type 2) AC infected by C.albicans	One commissure treated with 100,000 IU/g Nystatin ointment 4 times daily for one month	Treatment group: 8/8 sites healed after 4 weeks; no growth of C.albicans one week after disappearing of the lesions
			Contralateral commissure treated with placebo 4 times daily for one month	Placebo group: 1/8 sites healed after two weeks; C.albicans detected in each one of the remaining lesions (7/8)
<b>Cross and Short (2008)</b>	Small case-series	2 pediatric pts with grade 2 AC while under fixed orthodontic treatment	Miconazole nitrate 2% 4 times daily for two weeks	Complete remission after one session for one patient; unresponsiveness to two sessions of myconazole for the other patient, leading to suspension of fixed orthodontic treatment
<b>da Cunha Filho et al, (2014)</b>	Case-report	58 y-o man with plasma-cell AC of the right commissure, unresponsive to antibiotic, topical antifungals,	Pimecrolimus twice daily for 90 days	Partial improvement, although a complete remission could not be achieved after two years

---

infiltration with  
triamcinolone,  
cryosurgery

---

<b>Kumar et al (2016)</b>	Clinical trial	10 pts with AC – no details regarding clinic and/or microbiologic features	Ozonized olive oil applied twice daily	Healing reached within 2.3 days – no further details in terms of follow-up visits
---------------------------	----------------	----------------------------------------------------------------------------	----------------------------------------	-----------------------------------------------------------------------------------

---

**AC:** angular cheilitis; **IU:** International Unit; **Pts:** patients; **U:** Unit; **y-o:** years old.

Author Manuscript

**Table 2.** Available studies for OVD restoration techniques as treatment of AC

Reference	Type of study	Size of sample	Treatment provided	Main findings
Symingtn et al (1971)	Case-series	8 pts edentulous pts with dentures affected by AC unresponsive to antifungal creams	Surgical excision of the area affected by AC; closure of the surgical defect with rotated, raised vertical mucosal flap In six cases surgery performed under general anesthesia	7 pts displayed post-operative healing  5 showed no recurrence after two years
Chernosky (1985)	Case-report	2 pts with decreased OVD and AC	Injection of 2 ½ vials of purified bovine collagen implant (Zyderm®) nine times in a 6-months period for patient n.1  Injection of two vials of purified bovine collagen implant (Zyderm®) on three occasions over a period of 2 months for patient n.2	No reoccurrence after 8 months for patient n.1  No reoccurrence after 3 months for patient n.2
Lorenzo-Pouso et al. (2018)	Case-report	80 y-o patient with recurrent bilateral AC reluctant to prosthodontics treatment	After bilateral intraoral mental nerve block, hyaluronic acid dermal filler (Surgiderm 30; Inibsa) was injected in both mentolabial sulci with a 28-gauge needle	Immediate relief with no recurrence of AC in the next 12 months

AC: angular cheilitis; OVD: occlusal vertical dimension; Pts: patients; y-o: years old.

**Table 3.** Available studies for alternative treatments of AC

Reference	Type of study	Size of sample	Treatment provided	Main Findings
<b>Murphy and Bisada (1979)</b>	Case-report	25 y-o three-months pregnant woman with iron deficiency anaemia and AC	Two capsules of ferrous sulphate twice daily Duration: six months?	Disappearance of AC and no recurrence
<b>Lu (2007)</b>	Case-report	87 y-o woman with recurrent AC and drooling of saliva persisting for four years	Mandibular removable prosthesis, combined with a catheter device in the posterior left flange to prevent drooling, and redirect saliva in the oropharynx	Ceasing of drooling and no recurrence of AC
<b>Rocha et al (2016)</b>	Case-report	28 y-o man with AC after 19 days of chemotherapy with methotrexate for acute lymphoblastic leukemia	Nystatin 100,000 IU/ml, miconazol gel 2% four times daily, combined with aPDT (application of Methylene Blue 0.01% for five minutes, continuous diode laser irradiation, 660 nm, 120 J/cm <sup>2</sup> , 120s, 4.8J, 40mW, 1W/cm <sup>2</sup> , spot size 0.04 cm <sup>2</sup> ) and LLLT (660nm, 10J/cm <sup>2</sup> , 40mW, 0.4J and 10s/per point)	Immediate disappearance of pain right after aPDT application Improvement of wound healing and pain after LLLT (VAS going down to 0 after laser irradiation)

**AC:** angular cheilitis; **aPDT:** antimicrobial Photodynamic Therapy; **IU:** International Unit; **LLLT:** low-level laser therapy; **VAS:** Visual Analogue Scale; **y-o:** years old.